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## Neurological soft signs in schizophrenia and mood disorders

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# CHAPTER 8

## **DISCUSSION AND CONCLUSION**

Despite extensive research in the past decades our knowledge on neurological soft signs (NSS) has only showed limited progress and the exact meaning of NSS has remained obscured. Two domains of explanations for this limited progress can be distinguished. Firstly the methodological issues such as measurability and reliability. Secondly issues relating to the often complex relationships between NSS and a broad variety of confounding variables such as IQ, age, diagnosis, handedness, premorbid functioning, obstetric complications, tardive dyskinesia, catatonia and so on. In our introduction we discussed the potential suitability of NSS as an endophenotype for schizophrenia based on criteria of measurability, reliability and specificity.

### **MEASURABILITY**

As pointed out in the introduction, the assessments of NSS have vastly improved over time with the introduction of standardised assessments. In the past decade numerous tools have been developed for the assessment of NSS. However to date there is no consensus on exactly which signs should be incorporated in NSS assessments. Among others there is debate on the inclusion of EPS and TD signs and on the inclusion of primitive reflexes and eye movement disorders. Assessments also vary regarding the sequencing and motor coordination tests. As a consequence the number of signs varies between assessments and particularly motor coordination signs (Manschreck et al. 1985; Walker 1981) and sensory signs (Kinney et al. 1999; Martin et al. 1995) have been the focus of separate studies. To date the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989) is the most frequently used but has substantial overlap with the Cambridge Neurological Investigation (CNI) (Chen et al. 1995) which is the most comprehensive. The use of the CNI in our studies did allow us to study the broadest variety of signs, the trade off being that our data was not comparable with the majority of studies. A more obscured issue regarding measuring NSS is that of the type of outcome variable. The NES and the CNI and most other assessments measure NSS on an ordinal scale (ie. absent, unclear, present, marked). This process of rating is subject to measurement bias (chapter 2). The scores are subsequently transformed to either total scores or scores on categories of signs. To avoid multiple comparison-issues generally the sum-scores are used for statistical testing. However the compositions of these categories are debatable. In our literature review we could not find a clear pattern of NSS based on the specificity of NSS for schizophrenia (chapter 5). However the categories of NSS we derived by means of a principle component analysis of those signs distinguishing patients from controls, revealed a pattern of NSS that was related to established abnormalities in schizophrenia but deviated from traditional categories of NSS (chapter 6). The lack of clarity regarding the inclusion of NSS in the assessments therefore adversely affects the measurability.

Because the majority of subjects under study will have only a limited number of NSS the scores on the majority of signs will be zero. As a consequence the distribution of the outcome measures of NSS assessments will be seriously skewed and depart from normality and have a substantial measurement error. As an endophenotype this provides a serious disadvantage compared to alternative endophenotypes such as fMRI abnormalities. In this respect it is interesting to note a promising new development in the rediscovery of some early assessment tools for movement disorders as a means to assess NSS such as a computerised pin board (Henkel et al. 2004).

## RELIABILITY

Reliability can be broadly divided in test-retest reliability and inter-raters reliability. We measured NSS simultaneously by two raters and calculated measures of consistency between raters, which ranged from poor to good for the categorical scores and was good for the overall score (chapter 2). Establishing the test retest reliability of NSS is considerably more complicated and is related to issues of temporal stability of NSS and the relationships of NSS with symptoms, medication and other confounding variables. If NSS are to provide an endophenotype for schizophrenia the NSS should represent a stable trait independent from changeable confounders such as medication, movement disorders and symptoms. However in contrast to the required independence of NSS from medication some studies did find effects of prolonged medication exposure on NSS (King et al. 1991; Gupta et al. 1995). This is likely to be the result of the fact that extra-pyramidal signs and tardive dyskinesia signs are influenced by medication and consequently NSS are subject to change in those NSS assessment scales that include EPS and TD signs. It also seems plausible that NSS that are related to EPS and TD signs such as motor-sequencing tasks show a relationship with medication as indeed was found by Egan et al. (Egan et al. 2001). In contrast, the majority of studies into the effect of medication on NSS have argued against such a relationship (Ismail et al. 1998; Heinrichs and Buchanan 1988) and increased NSS have also been reported in medication naïve schizophrenia patients (Venkatasubramanian et al. 2003). We studied the relationship between antipsychotic medication and NSS by means of a cross sectional study where we compare the influence of atypical and classical antipsychotic drugs on NSS, TD and EPS in a group of first episode psychosis patients (chapter 4). We found that the number of NSS was not influenced by the type of medication insofar they did not incorporate TD signs. However the type of medication did influence the number of TD signs. It is therefore likely that NSS are independent from medication insofar the assessments do not incorporate EPS and dyskinesia signs.

The relationship between symptom profile and NSS has been investigated extensively with contradicting results. Studies presenting an association between NSS and symptom severity or profile (Tucker et al. 1975; Manschreck et al. 1981; Manschreck et al. 1981; Braun et al. 1995; Manschreck et al. 1981; Manschreck and Ames 1984; Wong et al. 1997; Browne et al. 2000; Flashman et al. 1996) are balanced by studies refuting this (Flyckt et al. 1999b; Kolakowska et al. 1985; Sanders et al. 1994; Merriam et al. 1990). We explored the relationship between symptom profile and NSS in patients with first episode schizophrenia and found the NSS to be independent from symptom profile (see chapter 6). Overall it is noteworthy that the relationship between movement disorders and negative symptoms is much better documented (Pantelis et al. 2001; Van Os et al. 1997) and that in this respect NSS differ from movement disorders.

Age is another potential confounder and changeable by definition. A relationship with NSS is suggested by studies presenting increased numbers of NSS in elderly patients (Jenkyn et al. 1985). Until recently few longitudinal studies have been published (Smith et al. 1999; Torrey 1980; Chen et al. 2000) predominantly in patients with chronic schizophrenia. However very recently, 2 studies have been published (Chen et al. 2005; Emsley et al. 2005) likely the result of increased interest in NSS as an endophenotype for the vulnerability to schizophrenia. We found no significant changes in the numbers of NSS 2-years after a first episode of psychosis.

However, the number of NSS was increased in patients with an increase of medication. These findings concur with the majority of the evidence suggesting that NSS do show temporal stability, but subsets of NSS may show variation related to symptom profile and clinical outcome

In the introduction we already discussed the theoretical relationship between movement disorders and NSS. Whereas the relationship with medication is thoroughly investigated, the relationship with movement disorders is not. Direct comparison of patients with TD and those without revealed no significant differences with regard to the presence of neurological “soft” signs (Gureje 1987) (chapter 4). In contrast, primitive reflexes, a category sometimes included in NSS have been found to be related to TD (Youssef and Waddington 1988). The scarcity of studies into the relationship between NSS and movement disorders and the similarities between them emphasizes the need for further study into the question whether EPS and TD are the result of a similar neurodevelopmental vulnerability as NSS and to what extent there is overlap and separation of the underlying processes.

Although with the above the most apparent confounders are discussed the list of potential confounders is longer and the discussion beyond the scope of this thesis. Other potential confounders include among others; alcohol and substance abuse (Douyon et al. 1998; Keenan et al. 1997), cognitive function, premorbid adjustment, aggression, acathesia, family loading for schizophrenia, neuroticism, negative symptoms, aggression, disorganisation.

## **SPECIFICITY**

Numerous studies have found NSS in a vast variety of psychiatric disorders apart from schizophrenia and mood disorders. NSS have been reported in alcoholism, PTSD, senescence, bipolar disorder, trichotillomania, violent adolescents and so on. Similar to the poor specificity of the majority of findings in schizophrenia such as neuropsychological measures, this does not rule out a pattern of symptoms in which NSS or categories of NSS may be more prevalent in schizophrenia compared to healthy controls and other psychiatric disorders. Because of the lack of studies comparing two diagnostic groups we studied NSS in schizophrenia and mood disorders and healthy controls in order to investigate the specificity of NSS for schizophrenia and mood disorders. In our review we found that NSS are also apparent in mood disorders, at intermediate level between schizophrenia and controls (chapter 5). We did find a subset of NSS that did show specificity for schizophrenia compared to mood disorders (chapter 6) but this finding need to be interpreted with caution. We included eye movement disorders in that group and the measurability of these signs is likely to have been poor in the absence of suitable equipment. Moreover the findings await replication in a new dataset before any firm conclusions can be drawn regarding their specificity. In analogy with the poor specificity of the majority of findings in schizophrenia we therefore conclude that generally NSS do not show specificity for schizophrenia although the number of NSS or categories of NSS may differ between diagnostic groups.

## **SUITABILITY OF NSS AS AN ENDOPHENOTYPE FOR SCHIZOPHRENIA**

In this thesis we outlined the three main criteria for the suitability of NSS as an endophenotype for schizophrenia. Regarding measurability we pointed to the main flaws being the diverse composition of the assessments and categories of signs in addition to the less than perfect type of data output. Regarding the reliability we concluded that although the interrater reliability for the categories of signs is acceptable, the interrater reliability for single signs is much worse. In addition there is some evidence suggesting temporal instability of NSS in a specific group of schizophrenia patients, most likely those with a poor outcome (who potentially have a high genetic loading). However the main problem with NSS as an endophenotype is the poor specificity of NSS for schizophrenia. The overall conclusion should therefore be that although NSS continue to show some potential as an endophenotype, the evidence listed here suggests that it is unlikely to provide an endophenotype for schizophrenia.

## **LIMITATIONS**

Several limitations of this thesis must be pointed out. A limitation that our studies share with most studies is its case-control design. Only few longitudinal studies have been published (see chapter 3). All of these studies are naturalistic follow up, with limited (if any) medication change. Since the majority of studies suggest that there are no changes in the number of NSS, studies venturing into establishing this will face issues of power when trying to disprove change in NSS levels.

The power of our study is one of the main problems of this study. As a result of the large number of variables even a substantial sample size as used in these studies has too limited power to effectively control for the extensive numbers of possible confounders. This problem is aggravated by the relative imprecise measure of NSS, which resulted in bigger standard deviations and skewed non-normal distribution and thus further decreased the power. Also we did not include a substantial number of affective psychosis patients in our sample and consequently are unable to investigate NSS in this specific group and particularly the potential differences in NSS in affective psychosis compared to schizophrenia. However, in hindsight the major flaw in the design of this thesis is the lack of information on family history of psychosis of our patients. As a result we were unable to test our hypothesis that an increase of obstetric complications and a need for increased medication at two years follow up are related to differences in family loading for schizophrenia and that NSS are a reflection of vulnerability to schizophrenia.

## **GENES AND ENVIRONMENT**

In an attempt to illuminate the meaning of NSS we will discuss genetic and environmental influences on NSS. Evidence for the association of NSS with genes can be found from several sources. Firstly from twin studies; studies in identical twins and dizygotic twins can provide an estimate of heritability of NSS. However to date only studies in identical twins discordant for

schizophrenia have been published (Cantor Graae et al. 1994; Mosher et al. 1970; Mosher et al. 1971; Niethammer et al. 2000; Stabenau and Pollin 1967; Torrey et al. 21994; Weinberger et al. 1992; Werry et al. 1971). The strongest evidence from twin research comes from the study of Niethammer (2000); they compared identical discordant twins with unaffected twins and found the NSS to be increased in the well discordant twins compared to the unaffected twins, a finding consistent with the other studies.

Further evidence can be obtained from family studies in siblings and children of schizophrenia patients (Egan et al. 2001; Flyckt et al. 1999a; Ismail et al. 2000; Kinney et al. 1986; Kinney et al. 1999). Without exception these studies found increased NSS in relatives of schizophrenia patients, compared to subjects without a family history of psychosis. Further evidence for a genetic background may be found in adoption studies and linkage or association studies but to date no such studies have been published. Discussing environment triggers a semantic and theoretical discussion on exactly what can be defined as environmental influence. Medication may be considered an environmental influence, but may also be related to genes. For sake of this discussion we will review environmental influences using a broad definition of environment. Compelling evidence suggests that the number of NSS or at least categories of NSS are subject to fluctuation and influenced by environment. We found the number of neurological signs to be dependent on the number of obstetric complications (see chapter 7). Moreover changes in the number of NSS were present in those patients that had a medication increase at two years follow up. Finally we also found that TD signs, which were included in our NSS assessment, did in fact show a relationship with the type of antipsychotic drug, classical versus atypical. Moreover it is likely that alcohol abuse influences NSS. And finally there are the environmental influences on schizophrenia that may also influence NSS. There is therefore suggestion of both genetic and environmental influences on NSS but any clear relationship has remained obscured. One explanation could be that NSS are a heterogeneous group of symptoms with several neuropathological processes that have separate and often independent relationships that may cross traditional diagnostic boundaries and definitions. However we like to add another possibility as an explanation for the limited progress in the investigation of NSS. The multiple, complex and often contradicting findings in NSS research could be the consequence of gene-environment interaction (GEI). Whereas evidence suggests a GEI between schizophrenia and cannabis abuse, urbanicity, season of birth and obstetric complications this list is far from exhaustive and further research is required into potential candidates such as migration, trauma, adverse life events, maternal deprivation and perhaps NSS.

## **FUTURE DIRECTION**

Our findings warrant further investigation of a combination of movement and eye-movement abnormalities as a potential endophenotype for schizophrenia. This would need to include the use of standardised equipment for reducing measurement error. In addition further research in NSS could focus on NSS as a GEI. However, there are several methodological and conceptional issues in the research of GEI that need exploring. Broadly speaking GEI are divided in shared- and non-shared environmental influences. Shared environmental influences are those environmental circumstances that are shared between siblings (for instance social economic status) in contrast to non-shared environmental influences such as trauma. Because of the nature of the

shared environmental influences these are hard to investigate and traditionally the emphasis has been put on non-shared environment. However this is questionable for three reasons. Firstly, there is no reason to assume that environmental factors that are shared are any less influential. Urbanicity is an interesting example in that respect. Its influence is established but will be shared in siblings in the major part of the first two decades of their lives. Secondly because several of the polymorphic alleles that are investigated are extremely common (e.g. 40-50 % for COMT val/val polymorphism) which seems an encouragement to also look at common environmental factors. Finally because the rarity of several non-shared environmental factors in contrast to the commonness of some of the alleles increases the probability of detecting an association with genotypes, but not with environmental exposures. A second problem in the research into GEI is of a more methodological nature and is related to measurement error. Genotyping is in fact much more accurate than the vast majority of methods used to measure environmental exposures. This implies a lower degree of error, which in turn means an easier identification of associations with disease compared to environmental factors.

Broadly 4 methods for further NSS research can be considered. Firstly, the estimation of heritability of non-shared environmental factors in cohorts of identical and fraternal twins can provide insight in GEI for NSS. This method depends heavily on a mathematical approach and the ability to successfully identify and model the appropriate co-variables. Secondly adoption studies can provide a measure for the genetic background of NSS and are particularly interesting because they are able identify GEI with environmental factors that otherwise might have been contributed to shared environment (eg urbanicity). Thirdly, an epidemiological approach can be chosen. After the identification of a candidate environmental pathogen and selecting a good candidate gene, the GEI can be tested in a case-control association design. Finally, an interesting approach can be the use of existing (birth) cohorts. This has the advantage that these often provide a wealth of excellent assessment of environment. By genotyping those subjects with a high number of NSS in the (birth) cohorts GEI between environmental factors such as obstetric complications and NSS be successfully tested.

## CONCLUSION

Neurological soft signs show multiple and complex relationships with movement disorders, genetic loading for schizophrenia and diagnosis. Because of shortcomings in their measurability, reliability and particularly the specificity of NSS for schizophrenia they are unsuitable as an endophenotype for schizophrenia. However further research into a standardised automated measurement of a combination of movement and eye-movement abnormalities seem warranted. NSS may also provide a tool for the further study of the complex interplay between genes and environment. Considering the parallels and relationships with movement disorders they could thus contribute to the illumination of the role and pathology of movement disorders in schizophrenia and mood disorders.



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